REMARKS/ARGUMENTS

In response to the Office Action of July 31, 2006, Applicants have amended claims 1 and 9, and canceled without prejudice claims 2-8 and 10, which when considered with the following remarks, is deemed to place the present application in condition for allowance. Favorable consideration of all pending claims is respectfully requested.

In the office action, the Examiner has acknowledged Applicants' election without traverse of Group I, claims 1-8, drawn to a transgenic animal. The non-elected claims have been indicated in the listing of claims by the status identifier "withdrawn" or "withdrawn-currently amended." Claims 2-8 have been canceled without prejudice. Due to the amendments made to claim 1, Applicants respectfully request that claim 9 be rejoined with claim 1 since claim 9 is directed to the same subject matter and classified in the same class (class 800, subclass 13) as the subject matter of presently amended claim 1.

Claims 1-6 have been objected to as encompassing multiple inventions, in particular, transgenic and somatic recombinant animals. As presently amended, claim 1 is directed to transgenic animals. Claim 5 has been objected to as failing to further limit claim 1 when it reads on the elected invention. By this amendment, claim 5 has been canceled without prejudice as have claims 2-4 and 6. Withdrawal of the objection to claims 1-6 as applied to claim 1 is therefore respectfully requested.

Claims 1-8 have been rejected under 35 U.S.C.§ 112, second paragraph, as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. As suggested by the Examiner, claim 1 has been amended by inserting the phrase "whose genome" before "comprises." The Examiner has also found insufficient antecedent basis for the phrase "the soluble marker protein" in claim 8. As claim 8 has been canceled without prejudice by Applicants, the rejection of claim 8 is moot. Withdrawal of the rejection of claims 1-8 as applies to claim 1 is respectfully requested.

Claims 1-8 have been rejected under 35 U.S.C.§ 112, first paragraph, as allegedly directed to non-enabled subject matter. The position of the Examiner is that the specification is enabling for making and using a transgenic mouse whose genome comprises a nucleic acid molecule encoding a soluble marker protein inserted between a transcription start site and translation start site of an endogenous E-selectin gene. *See* office action, page 3. As presently amended, claim 1 recites: "A transgenic mouse whose genome comprises a polynucleotide

encoding a soluble marker protein functionally linked to a regulatory sequence of an endogenous gene encoding E-selectin wherein the polynucleotide encoding a soluble marker protein is inserted into a region of an E-selectin gene of a chromosomal E-selectin allele of the mouse, which is between a transcription start site and a translation start site of the E-selectin gene, wherein the mouse expresses the soluble marker protein by endothelial cells and the expression is regulatable by chemical or physical stimulus and wherein the polynucleotide comprises SEQ ID NO:11 or SEQ ID NO:12." In view of the amendments to claim 1, withdrawal of the rejection of claims 1-8 under 35 U.S.C. § 112, first paragraph, as applies to claim 1 is respectfully requested.

Claims 1-8 have also been rejected as allegedly not meeting the written description requirement of 35 U.S.C. §112, first paragraph. The Examiner's position is that the specification describes only a single species of knock-in mouse containing the soluble marker protein SEAP, in between the transcriptional and translatable start site of the E-selectin gene and which exhibits a specific phenotype, expression and secretion of the marker upon cytokine stimulation.

As discussed above, claim 1 has been amended to recite: "A transgenic mouse whose genome comprises a polynucleotide encoding a soluble marker protein functionally linked to a regulatory sequence of an endogenous gene encoding E-selectin wherein the polynucleotide encoding a soluble marker protein is inserted into a region of an E-selectin gene of a chromosomal E-selectin allele of the mouse, which is between a transcription start site and a translation start site of the E-selectin gene, wherein the mouse expresses the soluble marker protein by endothelial cells and the expression is regulatable by chemical or physical stimulus and wherein the polynucleotide comprises SEQ ID NO:11 or SEQ ID NO:12." In view of the amendments to claim 1, withdrawal of the rejection of claims 1-8 under the written description requirement of 35 U.S.C. § 112, first paragraph, as pertains to claim 1 is respectfully requested.

Claims 1-8 have been rejected under 35 U.S.C.§ 103(a) as allegedly unpatentable over Contag et al. (U.S. Patent No. 6,217,847) in view of Yang et al. (1997) *BioTechniques* 23:1110-1114. Contag et al. has been cited for teaching methods for detecting and localizing light originating from a mammal and animal models of disease states for localizing and tracking the progression of disease or a pathogen within the animal, and for screening putative therapeutic compounds effective to inhibit the disease or pathogen. Column 15, paragraph 4 of Contag et al., teach:

> In a related aspect, a promoter expressed in certain disease states can be used to mark affected areas in a transgenic animal, and expression of the light-generating moiety can be used to monitor the effects of treatments for the disease state. For example, E-selectin is expressed at sites of inflammation in vivo (Pober and Cotran, 1991, Lab. Inves. 64:301-305). Accordingly, the E-selectin promoter can be isolated and used to drive the expression of a luciferase gene.

The Examiner readily admits that Contag et al. do not teach a transgenic mouse whose genome contains an E-selectin promoter operably linked to a secreted alkaline phosphatase (SEAP). *See* office action, page 11, final sentence.

Applicants respectfully submit that Contag et al. relates to the non-invasive methods for detecting, localizing and tracking progression of infection diseases in an animal model (*see e.g.* column 1, line 45), integration of a transgene in a mammalian subject (column 2, lines 60-63), detecting localization of promoter induction event (column 3, lines 15-19), identifying therapeutic compounds effective to inhibit spread of infection by a pathogen (column 3, lines 31-33) or to inhibit the growth and/or the metastatic spread of a tumor (column 4, lines 5-7). Contag et al. suggests the use of the E selectin promoter in order to "mark affected areas in a transgenic animal" an to "monitor the effects of treatments for the disease state ", i.e. to monitor or localize the "sites of inflammation in vivo". Contag et al. does not teach or suggest the monitoring of a specific gene expression, much less the E selectin gene.

Yang et al. has been cited for teaching a vector comprising a cDNA encoding SEAP; for teaching that the chemiluminescenced-based SEAP assay is about 10-fold more sensitive than similar assays using luciferase as the reporter enzyme; and for teaching that SEAP has the advantage over luciferase because SEAP is secreted into the culture medium, thus making it faster and easier to assay for its activity without disruption of cells.

It is respectfully submitted that there is no teaching or suggestion in Yang et al. for the use of a vector comprising a cDNA encoding a soluble marker protein (including SEAP), in order to generate a transgenic mouse expressing the soluble protein marker under the control of an E-selectin promoter, wherein the polynucleotide encoding a soluble marker protein is inserted into a region of an E-selectin gene of a chromosomal E-selectin allele of the mouse, which is between a transcription start site and a translation start site of the E-selectin gene, wherein the mouse expresses the soluble marker protein by endothelial cells, the expression is

regulatable by chemical or physical stimulus, and wherein the polynucleotide comprises SEQ ID NO:11 or SEQ ID NO:12, as presently claimed by Applicants.

According to the Examiner, it would have been obvious to one skilled in the art to use SEAP as a marker protein as taught by Yang et al., instead of luciferase (taught by Contag et al.), linked to the E-selectin promoter (taught by Contag et al.) in making a transgenic animal. One skilled in the art would have allegedly been motivated to do so since Yang et al. teach that SEAP is more sensitive than luciferase, and the ease of use of SEAP in either chemiluminescent or fluorescent assays. The Examiner further alleges that one skilled in the art having such motivation would also have had a reasonable expectation of success since Contag et al. teach a transgenic mouse containing a construct comprising E-selectin promoter operably linked to a luciferase reporter, and since Yang et al. teach a plasmid vector comprising SEAP cDNA and provide the alleged motivation to use SEAP as a marker protein.

In the first instance, Applicants respectfully submit that there is no motivation in either of the cited references to combine the teachings provided therein in the manner the Examiner has done. Contag et al is directed to non-invasive localization of a light-emitting conjugate in a mammal. Yang et al. is directed to using a chemiluminescence-based SEAP assay in a transformed cell culture and assaying the enzyme after secretion into the cell culture medium. Contag et al. involves the use of photodetector devices having a high enough sensitivity to enable the imaging of faint light from within the mammal. Such photodetector devices include e.g., "night vision" goggles, reduced-noise photodetection devices, photon amplification devices and image processors. Thus, the teaching by Yang et al. that SEAP has an advantage over luciferase because SEAP is secreted into the culture medium, thus making it faster and easier to assay for its activity without disruption of cells, is only relevant when considering other cell culture-based assay systems. Yang et al. therefore, would not have provided a skilled artisan having Contag et al. in hand, with any motivation to use SEAP as a marker protein since Contag et al. utilize live animals and not cell cultures, since Contag et al. do not utilize secretion of a light-generating protein into any culture medium, and since the use by Contag et al. of photodetector devices do not require disruption of any cells in the animal.

Applicants respectfully submit that *pro arguendo,* even if there was a motivation to combine the references in the manner the Examiner has done, one skilled in the art would still not arrive at Applicants' invention. Contag et al. only go so far as to teach a transgenic animal

containing an introduced E-selectin promoter operably linked to a luciferase gene. Even if there was a motivation to combine Yang et al. with Contag et al, such combination of teachings still would not have rendered obvious the idea of decreasing or preventing expression of the native E-selectin structural gene which occurs in the transgenic mouse of the present invention and which represents an improvement over the transgenic mouse of Contag et al. Further, there is no suggestion in the combination of Contag et al. with Yang et al for a transgenic mouse expressing the soluble marker protein by endothelial cells as presently claimed.

The present invention allows expression of a specific gene, i.e. an E selectin gene, to be assessed in a live animal, because this specific gene is a marker of endothelial cell activation, which is itself a marker of inflammatory condition and transplantation rejection. *See* specification, first paragraph. Assessing the expression of the E selectin gene *in vivo* allows the screening of potential therapeutic agents for the treatments of disorders associated with the E selectin gene expression, e.g. inflammatory conditions and transplantation rejection. In accordance with the present invention, the endogenous E selectin coding region is replaced by a coding region for a protein whose expression can be assessed by a simple and sensitive enzyme assay, i.e. SEAP. If, as in Contag et al., the endogenous gene is not knocked out in the host animal, the endogenous selectin gene can also be expressed and it would not be possible to make any link between the production of SEAP protein and the activation of the E selectin gene, and thus to assess the potential therapeutic effect of the agent to be tested.

Accordingly, based on the presently amended claims and the remarks hereinabove, the obviousness rejection can only be maintained using the benefit of hindsight reconstruction. Withdrawal of the rejection of claims 1-8 under 35 U.S.C. § 103(a) as applied to claim 1 is therefore warranted.

Claims 1-8 have been rejected on the ground of nonstatutory obviousness-type double patenting as allegedly unpatentable over claim 1 of U.S. Patent No. 6,632,978. Applicant will consider filing a terminal disclaimer upon allowance of the pending claims; it is therefore requested that the rejection be held in abeyance until such time.

In view of the foregoing remarks and amendments, it is respectfully submitted that the present application is in condition for allowance, which action is earnestly solicited.

Respectfully submitted,

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